REMARKS

Formal Matters

Claims 28-30 are pending in the application. Claims 27 and 31 have been canceled without prejudice to later prosecution. Claim 30 is amended. No new matter is added by the amendments. Support for the amendments is found throughout the specification and in previously pending, now canceled, claims 27 and 31.

Claim 29 has been withdrawn from consideration due to a species election. Applicants demonstrate herein that the generic claims are patentable, and therefore request consideration of species claim 29 which depends from a generic claim.

Withdrawn Rejections

Applicants acknowledge withdrawal of rejections as specified on pages 2 and 3 of the Office action.

Rejections Maintained

Rejection Under 35 U.S.C. § 103(a) (Carter et al. and Morimoto et al.)

Claims 27 and 28 remain rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Carter et al. (US6054297, the "'297 patent) and further in view of Morimoto et al. (J. Biochem. Biophys. Methods (JBBM) 24:107-17 (1992)). Applicants respectfully traverse the rejection as applied and as it might be applied to the currently pending claims for the reasons provided below.

Claim 27 is canceled, rendering moot its rejection.

Claim 28 is drawn to a composition of claim 30 comprising a physiologically acceptable carrier and a mixture of incorrectly disulfide linked antibody fragment and correctly disulfide linked antibody fragment, wherein the purity of the correctly disulfide linked antibody fragment in the composition is at least about 95%, wherein the antibody fragment is selected from the group consisting of a $F(ab')_2$ fragment, Fab fragment, Fab' fragment and linear $F(ab')_2$ fragment, and wherein the antibody fragment binds $p185^{HER2}$.

The Carter '297 patent discloses and claims variant immunoglobulins, including humanized antibodies, and methods of making them. Humanized antibodies that bind HER2 are disclosed and claimed. The '297 patent does not, however, disclose a composition comprising a physiologically acceptable carrier and correctly and incorrectly disulfide linked antibody fragments wherein the purity of the correctly folded antibody fragment is at least about 95%.

Morimoto et al. discloses purification of $F(ab')_2$ fragments but does not disclose a composition comprising a physiologically acceptable carrier and correctly and incorrectly disulfide linked antibody fragments wherein the purity of the correctly folded antibody fragment is at least about 95% as claimed by Applicants.

As a result, the Carter '297 patent in view of Morimoto et al. fails to yield Applicants' invention as claimed in claim 28. Withdrawal of the rejection and allowance of the claim is respectfully requested.

Rejection Under 35 U.S.C. § 103(a) (Hudziak et al. and Morimoto et al.)

Claims 27 and 28 remain rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Hudziak et al. (WO89/06692) and further in view of Morimoto et al. (*supra*). Applicants respectfully traverse the rejection as applied and as it might be applied to the currently pending claims for the reasons provided below.

Claim 27 is canceled, rendering moot its rejection.

Claim 28 is drawn to a composition of claim 30 comprising a physiologically acceptable carrier and a mixture of incorrectly disulfide linked antibody fragment and correctly disulfide linked antibody fragment, wherein the purity of the correctly disulfide linked antibody fragment in the composition is at least about 95%, wherein the antibody fragment is selected from the group consisting of a $F(ab')_2$ fragment, Fab fragment, Fab' fragment and linear $F(ab')_2$ fragment, and wherein the antibody fragment binds $p185^{HER2}$.

Hudziak et al. (WO89/06692) discloses a method of inhibiting growth of tumor cells which overexpress a growth factor receptor or growth factor by treating cells with antibodies which inhibit the growth factor receptor function. Anti-HER2 monoclonal antibodies are disclosed. The Hudziak et al. (WO89/06692) application does not, however disclose a

composition comprising a physiologically acceptable carrier and correctly and incorrectly disulfide linked antibody fragments, as claimed by Applicants, wherein the purity of the correctly folded antibody fragment is at least about 95%.

Morimoto et al. discloses purification of $F(ab')_2$ fragments but does not disclose a composition comprising a physiologically acceptable carrier and correctly and incorrectly disulfide linked antibody fragments, as claimed by Applicants, wherein the purity of the correctly folded antibody fragment is at least about 95%.

As a result, the Hudziak et al. (WO89/06692) in view of Morimoto et al. fails to yield Applicants' invention as claimed in claim 28. Withdrawal of the rejection and allowance of the claim is respectfully requested.

New Rejections

Rejection Under 35 U.S.C. § 102(b) (Morimoto et al.)

Claims 27 is rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Morimoto et al. Applicants respectfully traverse the rejection as applied and as it might be applied to the currently pending claims for the reasons provided below.

Claim 27 is canceled, rendering moot its rejection. Withdrawal of the rejection is respectfully requested.

Rejection Under 35 U.S.C. § 102(b) (Neblock et al.)

Claims 27 and 30-31 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Neblock et al. Applicants respectfully traverse the rejection as applied and as it might be applied to the currently pending claims for the reasons provided below.

Claims 27 and 31 are canceled, rendering moot their rejection. Withdrawal of the rejection of claims 27 and 31 is respectfully requested.

Claim 30 is drawn to a composition comprising a physiologically acceptable carrier and a mixture of incorrectly disulfide linked antibody fragment and correctly disulfide linked antibody fragment, wherein the purity of the correctly disulfide linked antibody fragment in the

composition is at least about 95%, wherein the antibody fragment is selected from the group consisting of a $F(ab')_2$ fragment, Fab fragment, Fab' fragment and linear $F(ab')_2$ fragment.

Neblock et al. discloses thioether-cross-linked bispecific F(ab')2 monoclonal antibodies and methods of making them (see pages 128-129 (Results section) of Neblock et al.). The mixture disclosed in the paragraph bridging pages 128 and 129 of Neblock et al. contains a thioether-cross-linked bispecific $F(ab')_2$ present at approximately 93%, not a composition as in Applicants' claim 30 comprising a correctly disulfide linked antibody fragment where, as Applicants disclose on page 9 of the specification, all cysteine residues in the antibody are covalently associated as disulfide bonds and these disulfide associations correspond to the disulfide associations of the native immunoglobulin.

As a result, Neblock et al. fails to anticipate Applicants' invention as claimed in claim 30. Withdrawal of the rejection and allowance of the claim is respectfully requested.

Rejection Under 35 U.S.C. § 103(a) (Neblock et al. and Shalaby et al.)

Claim 27-28 and 30-31 is rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Neblock et al. (*supra*) as applied to claims 27 and 30-31 above and further in view of Shalaby et al. (J. Exp. Med. 175:217-225 (1992)). Applicants respectfully traverse the rejection as applied and as it might be applied to the currently pending claims for the reasons provided below.

Claims 27 and 31 are canceled, rendering moot their rejection. Withdrawal of the rejection of claims 27 and 31 is respectfully requested.

Claim 30 is drawn to a composition comprising a physiologically acceptable carrier and a mixture of incorrectly disulfide linked antibody fragment and correctly disulfide linked antibody fragment, wherein the purity of the correctly disulfide linked antibody fragment in the composition is at least about 95%, wherein the antibody fragment is selected from the group consisting of a $F(ab')_2$ fragment, Fab fragment, Fab' fragment and linear $F(ab')_2$ fragment. Claim 28 is drawn to the composition of claim 30 wherein the antibody fragment binds $p185^{HER2}$.

The Neblock et al. reference and its deficiencies are described above. Neblock et al. does not disclose a composition comprising a correctly disulfide linked antibody fragment having a purity of at least about 95%.

Shalaby et al. discloses a humanized bispecific antibody that binds HER2. It fails to disclose the composition of claim 30 or claim 28, which depends from claim 30.

Neblock et al. in view of Shalaby et al. fails to yield Applicants' claimed invention comprising a correctly disulfide linked antibody fragment, where correctly disulfide linked refers to disulfide associations corresponding to the disulfide associations of the native immunoglobulin.

The rejection having been overcome, withdrawal of the rejection and allowance of the claims is respectfully requested.

SUMMARY

Claims 28-30 are pending in the application. Claims 27 and 31 are canceled without prejudice to later prosecution.

Applicants have overcome the maintained rejections under Section 103(a) and new rejections under Sections 102(b) and 103(a). Withdrawal of the rejections and allowance of the claims is respectfully requested. In light of having demonstrated that the generic claims are patentable, consideration of claim 29 is respectfully requested.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is strongly encouraged to call the undersigned at the number indicated below.

This response/amendment is submitted with a transmittal letter and petition for a three-month extension of time and fees. In the unlikely event that this document is separated from the transmittal letter or if fees are required, applicants petition the Commissioner to authorize charging our Deposit Account 07-0630 for any fees required or credits due and any extensions of time necessary to maintain the pendency of this application.

Applicants respectfully request that a timely Notice of Allowance be issued in this case.

Respectfully submitted,
GENENTECH, INC.

Date: October 14, 2003

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Doc # 142822

Clean Set of All Pending Claims

October 14, 2003

28. (Once Amended) The composition of claim 30 wherein the antibody fragment binds $p185^{HER2}$.

29. (Once amended) The composition of claim 30 wherein the antibody fragment binds CD18.

30. (Once Amended) A composition comprising a physiologically acceptable carrier, and a mixture of incorrectly disulfide linked antibody fragment and correctly disulfide linked antibody fragment, wherein the purity of the correctly disulfide linked antibody fragment in the composition is at least about 95%, and wherein the antibody fragment is selected from the group consisting of a $F(ab')_2$ fragment, Fab fragment, Fab' fragment and linear $F(ab')_2$ fragment.